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Abstract: BACKGROUND The relationship between body mass index (BMI) (weight (kg)/ height(m)) and serious non-AIDS events is not well understood. METHODS We followed D:A:D study participants on antiretroviral therapy from their first BMI measurement to the first occurrence of the endpoint or end of follow-up (N=41,149 followed for 295,147 person-years). The endpoints were cardiovascular disease (CVD); diabetes; non-AIDS-defining cancers (NADCs) and BMI-NADCs (cancers known to be associated with BMI in general population); and all-cause mortality. Using poisson regression models, we analysed BMI as time-updated, lagged by 1 year, and categorized at: 18.5, 23, 25, 27.5 and 30 kg/m. RESULTS Participants were largely male (73%) with the mean age of 40 years (SD 9.7) and baseline median BMI of 23.3 (IQR: 21.2-25.7). Overall, BMI showed a statistically significant J-shaped relationship with the risk of all outcomes except diabetes. The relative risk (RR) for the BMI of <18.5 and >30 (95% CI) compared to 23-25, respectively, was as follows: CVD: 1.46(1.15-1.84) and 1.31(1.03-1.67); NADCs: 1.78(1.39-2.28) and 1.17(0.88-1.54); 'BMI-NADCs': 1.29(0.66-2.55) and 1.92(1.10-3.36). For all-cause mortality, there was an interaction by gender (P<0.001): RR in males: 2.47(2.12-2.89) and 1.21(0.97-1.50); and in females: 1.60(1.30-1.98) and 1.02(0.74-1.42). RR remained around 1 for intermediate categories of BMI. The risk of diabetes linearly increased with increasing BMI (P<0.001). CONCLUSIONS Risk of CVD, a range of cancers, and all-cause mortality increased at low BMI (<18.5) and then tended to increase only at BMI>30 with a relatively low risk at BMI of 23-25 and 25-30. High BMI was also associated with risk of diabetes.

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Body Mass Index and The Risk of Serious Non-Aids Events and All-Cause Mortality in Treated Hiv-Positive Individuals: D:A:D Cohort Analysis

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Abstract

Background

The relationship between body mass index (BMI) ($\text{weight (kg)/ height(m}^2\text{)}$) and serious non-AIDS events is not well understood.

Methods

We followed D:A:D study participants on antiretroviral therapy from their first BMI measurement to the first occurrence of the endpoint or end of follow-up (N=41,149 followed for 295,147 person-years). The endpoints were cardiovascular disease (CVD); diabetes; non-AIDS-defining cancers (NADCs) and BMI-NADCs (cancers known to be associated with BMI in general population); and all-cause mortality. Using poisson regression models, we analysed BMI as time-updated, lagged by 1 year, and categorized at: 18.5, 23, 25, 27.5 and 30 kg/m^2 .

Results

Participants were largely male (73%) with the mean age of 40 years (SD 9.7) and baseline median BMI of 23.3 (IQR: 21.2-25.7). Overall, BMI showed a statistically significant J-shaped relationship with the risk of all outcomes except diabetes. The relative risk (RR) for the BMI of <18.5 and >30 (95% CI) compared to 23-25, respectively, was as follows: CVD: 1.46(1.15-1.84) and 1.31(1.03-1.67); NADCs: 1.78(1.39-2.28) and 1.17(0.88-1.54); 'BMI-NADCs': 1.29(0.66-2.55) and 1.92(1.10-3.36). For all-cause mortality, there was an interaction by gender ($P<0.001$): RR in males: 2.47(2.12-2.89) and 1.21(0.97-1.50); and in females: 1.60(1.30-1.98) and 1.02(0.74-1.42). RR remained around 1 for intermediate categories of BMI. The risk of diabetes linearly increased with increasing BMI ($P<0.001$).

Conclusions

Risk of CVD, a range of cancers, and all-cause mortality increased at low BMI (<18.5) and then tended to increase only at BMI >30 with a relatively low risk at BMI of 23-25 and 25-30. High BMI was also associated with risk of diabetes.

Key words: HIV; Obesity; BMI; AIDS; non-AIDS; all-cause mortality

INTRODUCTION

Excess weight is now increasingly prevalent in HIV-positive individuals receiving antiretroviral therapy (ART).^{1,2} While body mass index, BMI (measured as weight (kg)/height (m^2)) is an anthropometric measure and does not directly measure total body fat or biological markers of disease, it remains an easy and low-cost metric to screen for risk of certain conditions.³ However, in HIV-positive individuals, the relationship between BMI and various serious non-AIDS events (SNAEs) is not well studied.

In the general population, increasing BMI is associated with increased risk of various clinical outcomes including cardiovascular disease (CVD)³, diabetes mellitus (DM), several cancers such as those of gastrointestinal tract and endometrium,⁴ and all-cause mortality.⁵ Also, very low BMI has been associated with increased risk of mortality.⁵

HIV-positive individuals are unique in that they are exposed to ongoing inflammation/immune activation, ART toxicities, higher prevalence of life-style risk factors such as smoking and a higher overall risk of various SNAEs than general population.⁶ Further, BMI in this group is itself associated with immunosuppression and certain antiretroviral drugs among other factors.²

In one large cohort study BMI correlated strongly with CD4 count response to ART regardless of baseline CD4 count, with a highest CD4 count response at BMI levels of 25-30 but worse at higher or lower levels.⁷ On the other hand, weight gain following ART initiation has been shown to be harmful to cardio-metabolic health, especially in those with 'normal/overweight' weight at baseline.⁸ It is therefore possible that being HIV-infected modifies the relationship between BMI and various outcomes in this population. However, limited, if any, studies have rigorously evaluated BMI as a risk factor for non-AIDS outcomes.⁹ Better understanding of how BMI relates to SNAEs in HIV-positive individuals is therefore needed. This information will provide the key data to clinicians and the HIV community regarding the health implications of BMI—a well-known, easily and economically measured potential risk factor.

In this paper, we analysed the data from the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) study, a large heterogeneous cohort with well-validated outcomes and available data on a wide range of risk factors, to assess the relationship between latest BMI and the subsequent risk of various SNAEs and all-cause mortality.

METHODS

Study population and follow-up

The design of the D:A:D study has been described in detail elsewhere.¹⁰ In brief, it is an observational study of >49,000 HIV-positive people from 11 cohorts from Europe, Australia, and the USA. All participants were under active follow-up in their cohorts at the time of enrolment in the study. The primary study aim was to investigate the associations between use of ART and major non-AIDS events and death. Data are collected prospectively during routine clinic visits;

the standardized data set includes information on demographic factors, AIDS-related events, known risk factors for CVD, laboratory markers for monitoring HIV infection and CVD, and ART. Clinical events are regularly monitored and endpoints are centrally adjudicated.

In this study, we included all participants in the D:A:D cohort who had initiated ART, had at least one BMI measure available and at least one year of further follow-up from study entry. Follow-up commenced from the later of cohort enrolment or ART initiation or first BMI measurement. Non-AIDS cancers were collected systematically from 2004 and were therefore analyzed from 1st Jan 2004 onwards. Follow-up ended on the first occurrence of the respective endpoint or was censored at death or, 1st February 2014 or six months after last follow-up visit. All individuals had no pre-existing diagnoses of CVD, diabetes mellitus (DM) or non-AIDS cancers (NADCs) at study initiation.

Endpoints

The endpoints of interest were: (i) first CVD event, defined as the composite of myocardial infarction (MI), sudden cardiac death or invasive cardiovascular procedure (coronary artery bypass graft, carotid endarterectomy or angioplasty), or confirmed stroke; (ii) DM, defined as fasting glucose > 7.0 mmol/L on at least two occasions or a single value of NGSP haemoglobin A1c > 6.5%, or symptoms with a random glucose > 11.1 mmol/L, or 2-h oral glucose tolerance test > 11.1 mmol/L, or use of antidiabetic drugs (see www.chip.dk for details); (iii) NADCs (other than basal or squamous cell skin cancer, pre-cancers, and relapses); (iv) 'BMI-related NADCs' - a composite outcome of cancers thought to be associated with BMI in the general population (i.e. malignancies of oesophagus, pancreas, colon and rectum, breast, endometrium, kidney, thyroid and gallbladder)^{4,11}; and finally (v) All-cause mortality.

Statistical methods

BMI was the main exposure factor analysed as a time-updated variable lagged by 1-year (i.e. there was at least 1-year time-gap between last BMI measurement and the endpoint, so as to minimize bias from reverse causation) and categorised at the following clinical cut-offs: 18.5, 23, 25, 27.5 and 30 kg/m². The choice of strata was driven by the broad WHO BMI clinical cut-offs (underweight (<18.5), normal (18.5-25), overweight (25-30) and obese (>30))³, with additional cut-offs at 23 and 27.5 to better define the relationship. In sensitivity analyses, we also categorized BMI in deciles.

We used Poisson regression to model the relationship between BMI and each endpoint. Models were adjusted for key confounders not thought to be on the causal pathway for each respective endpoint. Potential confounders were identified using directed acyclic graphs (DAGs).¹² All variables, including age and CD4 count, were analyzed as time-updated (lagged by 1-year) where possible. In case a time-updated variable was not recorded at a given visit, previous known value was carried forward. A missing variable category was created for all variables to ensure all observations were included in models.

For CVD we adjusted for race (White/ Black/ Other/Unknown), sex, mode of transmission (sex between men/ injecting drug use/ sex between men and women/ other), family history of CVD, age, smoking status (current/ past/ never/ unknown), current abacavir use, cumulative protease inhibitor (PI) and nucleoside reverse transcriptase inhibitor (NRTI) use in years, and CD4 count (categorized as ≤ 200 , 201-350, >350 cells/mm³). For CVD outcome, we also present analysis from models additionally adjusted for variables thought to be on a causal pathway as identified in DAGs. These include lipids (total, HDL and LDL cholesterol), systolic blood pressure (SBP) and incident DM.

Similarly models for DM, NADC and all-cause mortality were adjusted for respective confounders (listed at the bottom of Figure-1 in 'Results'). Models for all outcomes were additionally adjusted for calendar year and clinical cohort. Finally, we also checked for interaction between BMI and sex for all outcomes.

The following sensitivity analyses were performed: (i) We categorized BMI according to the deciles of the distribution to allow for the more detailed examination of the relationship between BMI and outcomes; (ii) We lagged the BMI and all other time-updated variables by 2 years instead of one year and also analysed first measured BMI ('baseline' BMI) (to further minimize bias from reverse causation); (ii) and for the CVD and mortality outcomes, models were additionally adjusted for calculated creatinine clearance using the Cockcroft-Gault formula as decreased renal function has been associated with these outcomes.^{13,14} Since data on serum creatinine and weight were not available for a couple of cohorts, we only analysed these variables in sensitivity analysis.

All analyses were performed using STATA version 14 (STATA Corporation, College Station TX, USA).

RESULTS

Participant characteristics

A total of 41,149 individuals with 295,147 person-years of follow-up (PYFU) for the all-cause mortality outcome were included. PYFU varied for each outcome depending on follow-up time. Participants were largely male (73%) with baseline mean age of 40 years and median (IQR) BMI of 23.3 (21.2- 25.7). Table-1 shows key characteristics by baseline BMI category. Prevalence of

smoking and injecting drug use as mode of transmission appeared to be inversely related to the baseline BMI category, while mean total cholesterol and systolic blood pressure tended to positively correlate with BMI. During follow-up, BMI was measured at the median (IQR) of 6 months (4-9 months) interval. For all key confounders (including smoking, lipid levels, systolic blood pressure, hepatitis B and C status) a vast majority ($\geq 85\%$) of individuals had data recorded at least at some point during the follow-up. About 15% of individuals had unknown smoking status throughout the follow-up.

BMI and risk of SNAEs

Table-2 shows the number of people experiencing each outcome, and the incidence rates per 1000 PYFU. Figure 1 (panels a-d) shows incidence rate ratios (IRR or relative risk) from various models for all outcomes by time-updated BMI category. The BMI category of 23-25 was chosen as the reference category based on rates shown in Table-2. Overall BMI was a significant predictor for all outcomes (overall $P < 0.05$ for the BMI variable in all models). The relationship of BMI was *J* or *U*-shaped with the risk of all SNAEs except DM as detailed below. Also, the effect of BMI on all-cause mortality tended to vary by sex (P for interaction between BMI and sex for all-cause mortality: < 0.001) as shown in Table-2 (incidence rates) and Figure 1d (relative risks), but not for all other outcomes.

There were 1398 CVD events (rate: 4.8/1000 PYFU). Compared to those with a BMI of 23-25, IRR (95% CI) for those with a BMI of ≤ 18.5 was 1.46 (1.15 to 1.84), for 18.5-23 was 1.10 (0.96 to 1.27) and for > 30 , it was 1.31 (1.03 to 1.67), in the models adjusted for known confounders. Further adjustment for variables known to be on the causal pathway between BMI and CVD (such as SBP, and lipids) attenuated the relative risk at levels > 30 but not at BMI levels ≤ 18.5 or 18.5-23 (Fig 1a).

For DM, the relationship with BMI was linear, i.e. increasing risk with increasing BMI, with relative risk nearly 3.5 times (IRR 3.39, 95% CI: 2.79 to 4.12) for BMI>30 vs BMI of 23-25 (Fig 1b).

There were 1143 NADCs at a rate of 3.9/1000 PYFU of which 184 (rate: 0.6/1000 PYFU) were BMI-cancers. The IRR (95% CI) for NADC was highest for those with a BMI of ≤ 18.5 : 1.78 (1.39 to 2.28) and for those with a BMI of 18.5-23: 1.30 (1.11-1.53) and tended to be higher among those with a BMI>30 although the 95% CI crossed 1 (1.17, 0.88 to 1.54). However, for the BMI-cancers, BMI >30 was associated with nearly twice the risk compared to BMI 23-25 (IRR 1.90, 1.11 to 1.36) (Fig 1c).

Finally, the rates and IRR (95% CI) of all-cause mortality varied by sex. For males, the J-shaped relationship with BMI was more prominent. For males with a BMI of ≤ 18.5 , the relative risk of mortality was about 2.5 times (IRR 2.47, 2.12 to 2.89) higher and for those with a BMI of 18.5-23 IRR was 1.38 (1.23 to 1.54) compared to those with a BMI of 23-25. The risk then tended to increase only in those with BMI>30: 1.21, 0.98 to 1.50). For females, a BMI <18.5 was also strongly related with the risk of mortality but at a lower relative risk compared to that in males (IRR 1.60, 1.30 to 1.98) and the risk did not increase at higher levels of BMI (fig 1d). Of note, the follow-up data for females at BMI>30 was relatively small (about 8000 PYFU).

Sensitivity analyses

Supplementary Table-S1, <http://links.lww.com/QAI/B162> shows IRRs from all models with BMI categorised using the deciles of the distribution. Results were similar for all outcomes: for all SNAEs (except diabetes), relative risk was highest in the lowest 10% of the BMI distribution (equivalent to BMI<19.5) and tended to increase from the tenth decile (equivalent of BMI>28.7).

Lagging the BMI by 2 years (instead of 1) or analysing 'baseline' BMI instead on time-updated BMI broadly showed similar results (data not shown). Finally, data on creatinine were not uniformly available for all participants. Adjustment for creatinine clearance for CVD and all-cause mortality mildly attenuated IRRs for CVD but did not have any significant effect on the overall results or conclusions (data not shown).

DISCUSSION

In this longitudinal analysis of HIV-positive individuals enrolled in the DAD cohort, we found that the relationship between BMI and the risk of SNAEs including CVD, NADCs, 'BMI-related NADCs' and all-cause mortality was non-linear. In general, low BMI (<18.5, and also <23 in case of NADC and all-cause mortality in males) was associated with the higher risk of these SNAEs. Relative risk of SNAEs then only tended to increase again at BMI levels >30 which was most prominent for CVD, 'BMI-related NADC' and all-cause mortality in men. Finally, for diabetes, the risk increased in a linear fashion with increasing BMI, with relative risk nearly 3.5 times at BMI>30 compared to BMI of 23-25. Categorising BMI according to deciles of the distribution confirmed similar findings and broadly agreed with our choice of clinical cut-offs. Results were also robust to lagging BMI by 2 years or analysing baseline BMI to further minimise reverse causality.

Traditionally studies in HIV/AIDS examined BMI in the context of AIDS in the pre- or early ART era. Only a few recent studies have carefully examined BMI in the context of SNAEs in treated HIV-positive individuals. A study by Koethe et al with about 1200 HIV-positive participants in a single site cohort found that low BMI (<20) was associated with a higher risk of

composite of SNAEs, while intermediate BMI of around 25-30 and high BMI >30 was associated with lower or similar risk to BMI of 20-25.⁹ Our findings are broadly similar to those noted in the latter study; however, we did find elevated risk of several SNAEs at BMI>30. Of note, the relative risk at BMI>30 was small for most outcomes (ranging from 1.31 for CVD, 1.21 for all-cause mortality in men) but was nearly two- fold higher for 'BMI-related NADCs'. However, the study by Koethe et al only used BMI at baseline and did not have consistent data on smoking.

The finding that low BMI is associated with higher risk of death is consistent across studies even in the general population.⁵ In a large individual-data meta-analysis of nearly 4 million adults, BMI <18.5 was associated with about 1.8 fold higher risk of mortality in men compared to BMI of 22.5-25 after adjusting for smoking (corresponding IRR in our study was 2.47).⁵ This association was previously thought to be due to reverse causality (i.e. the disease affecting the BMI). However, in our study, this association remained even after ensuring the BMI precedes the outcome by at least 1 or 2 years. Also smoking tends to be inversely related to BMI and is an important confounder to account for.^{15,16} While our models adjusted for time-updated smoking, residual confounding from smoking cannot be ruled out. We also found higher risk of CVD in individuals with low BMI. Besides possible residual confounding by smoking, it is possible that people with low BMI get less aggressive disease prevention interventions compared to those with higher BMI. Our study did not collect health prevention or health behaviour data to be able to analyse this possibility. For the cancer outcomes, it is possible that weight loss starts several years prior to the diagnosis which may explain their associations with lower BMI.

Findings on intermediate to high BMI and all-cause mortality in the general population have tended to vary, although many of these studies did not adjust for smoking or had a shorter follow-up.^{5,17} However, the large meta-analysis described above, after adjustment for smoking, found relative risk of all-cause mortality in males to be around 1 for BMI 25 to 30, but increasing to 1.47 with BMI of 30-35, and to 2.0 in those with BMI>40.⁵ In our study, risk of all-cause mortality in males was high even at BMI of 18.5-23 (considered near optimal in general population), and then only tended to increase at BMI >30 in males. Relative to those with a low BMI, individuals with intermediate BMI tend to have greater muscle mass, exercise capacity and greater fat stores which may help in surviving stressful disease situations and confer survival advantage in sicker patients.¹⁸ Indeed, a large systematic review of patients with coronary artery disease at baseline found that mortality was highest at BMI <18.5 and lowest for those deemed 'overweight/mildly obese' (BMI ranges 25-30) and the risk increasing only at severely high BMI >35.¹⁹ A cohort study evaluating mortality after coronary bypass graft surgery found similar results.²⁰

We found that the BMI above 30 was associated with elevated risk of CVD which attenuated after adjustment for blood pressure, lipids and incident diabetes. Increasing BMI was also associated with increasing risk of diabetes. This suggests that high BMI could be a useful initial screening tool in individuals where detailed CVD risk factors are not known. Finally, though high BMI >30 was not associated with the higher risk of NADCs, it was associated with higher risk of 'BMI-related NADCs' with overall relative risk of around 2 (compared to BMI 23-25). In the general population, obesity is increasingly being recognised as the risk factor for several cancers, with reasonably consistent evidence for oesophagus, pancreas, colon and rectum, breast, endometrium, kidney, thyroid and gallbladder cancers.^{4,11} While the relative risk for specific

cancers varies, we did not have enough follow-up data to examine effect of BMI on specific cancers.

Our study benefitted from data on HIV-positive females. Findings were similar for females for all outcomes, except for all-cause mortality where the magnitude of risk at extremes of BMI in females was lower compared to males. A US cohort study on HIV-infected women found low BMI as predictor of mortality but not the high BMI (>25 or >30).²¹ Our findings on females in our cohort was consistent with this study. Of note, person-year data on females was limited especially at extremes of BMI which may have limited our power to analyse events in this subgroup.

The strengths of our study include a large heterogeneous cohort, with well-validated (through established protocols) outcomes and longitudinally measured BMI. Also, we were able to account for several key confounders in a time-updated fashion, including smoking and ART agents. Our study does have some limitations however. First, we did not have enough follow-up data and events at very high BMI levels (e.g. >35), which would have helped us further clarify the risks associated with severe obesity. Also, data on other risk factors such as health behaviors (e.g. diet/exercise) or preventive interventions (e.g. cancer screening) were not available. Moreover, other anthropometric measures such as waist:hip ratio which could be more accurate or supplement BMI were not available in this study. Also, even though our study designed ensured BMI measurements preceded diagnoses of SNAEs temporally, role of reverse causality cannot completely be ruled out given chronic nature of SNAEs. Finally, we could not perform a direct comparison between HIV-positive and negative individuals to better understand how BMI interacts with HIV or ART or population demographics and behaviour in determining outcomes.

In summary, we found that low BMI (≤ 18.5 , and in some cases 18.5-23) was associated with high risk of several individual SNAEs as well as all-cause mortality. The relative risk of SNAEs and mortality did not increase at intermediate/moderately high BMI (around 23-30) and only tended to increase at BMI >30 . These findings suggest that BMI of 25-30, thought to be 'overweight/mildly obese' in general population may in fact confer some survival advantage in HIV-positive individuals. Also, these findings seem to suggest that obesity at BMI >30 is likely harmful in the long-term even in HIV-positive individuals. Future studies should assess how short-term and long-term changes in BMI relate to the risk of SNAEs. Ultimately, whether change in BMI or weight gain or loss interventions (depending on current BMI) would actually improve outcomes in this population will need trials on carefully designed behavioral and nutritional interventions.

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D:A:D Participating Cohorts

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Fig-1: Latest BMI (lagged by 1 year) and the risk of SNAEs.

Footnote: All models adjusted for sex, race, mode of HIV transmission, clinical cohort, calendar year and time-updated age, smoking and CD4 count. Additional adjustments are as follows: Fig-1a: CVD: Model A additionally adjusted for being currently on abacavir, cumulative years on NRTIs and PIs. Model B: As model A plus additionally adjusted for time-updated (lagged by 1 year) diabetes, total, HDL and LDL cholesterol, systolic and diastolic blood pressure. Fig 1b: Models for diabetes adjusted for HCV infection and following time-updated (lagged by 1 year) variables: cumulative years of stavudine use, triglycerides, and HDL cholesterol. Fig 1c and Fig 1d: Models for cancer and all-cause mortality adjusted for hepatitis B or C co-infection. P for interaction between gender and BMI: <0.001 for all-cause mortality. BMI category of 23-25 was the reference category in all models.

Table-1: Baseline characteristics by baseline BMI category

	BMI (kg/m ²) category at baseline						
	<18.5	18.5-23	23-25	25-27.5	27.5-30	>30	Overall
N (%)	1929 (4.7)	17640 (42.9)	9283 (22.6)	6998 (17.0)	2910 (7.1)	2389 (5.8)	41149
Age in years (mean) (SD)	38.8 (9.8)	39.3 (9.3)	40.9 (9.8)	41.8 (9.9)	41.7 (10.2)	41.5 (10.3)	40.4 (9.7)
Male (%)	55.1	72	79.6	80.3	73.1	56.2	73.5
Infected with HIV through sex between men (%)	30.9	46.1	50.5	48.3	38.1	25.9	45
Infected with HIV through Injecting drug use (%)	24.9	17.1	13.4	11.2	9.9	9.9	14.7
Race- white (%)	47.6	52.5	51.2	50.2	45.9	39.4	50.5
Current smoker (%)	52.3	46	38.3	33.4	28.1	24.7	39.9
Family history of CVD (%)	6.6	6.7	7.1	7.2	5.7	7	6.8
CD4 count/mm³ (median) (IQR)	354 (205-535)	406 (269-600)	420 (284-610)	415 (277-601)	427 (290-614)	420 (283-635)	410 (273-635)
Log10 HIV RNA (copies/mL) (median) (IQR)	2.1 (1.7-3.9)	1.9 (1.7-3.8)	1.9 (1.7-3.7)	1.8 (1.7-3.7)	1.8 (1.7-3.6)	2 (1.7-3.8)	1.9 (1.7-3.8)
Hepatitis C coinfection (%)	29	21.7	18.1	14.9	13	12.5	18.9
Hepatitis B coinfection (%)	5.9	5.7	5.4	5.3	5.1	4.3	5.5
Total cholesterol mmol/L (mean) (SD)	4.7 (1.3)	4.9 (1.3)	5 (1.4)	5.1 (1.3)	5.2 (1.5)	5.1 (1.3)	4.9 (1.4)
HDL mmol/L (mean) (SD)	1.3 (0.5)	1.25 (0.5)	1.19 (0.4)	1.17 (0.4)	1.18 (0.5)	1.18 (0.4)	1.22 (0.4)
Systolic BP (mean) (SD)	115 (14.8)	120 (14.1)	124 (14.4)	126 (14.9)	128 (15.8)	129 (6.4)	123 (15.0)

Note: BP= blood pressure, CVD= cardiovascular disease, HDL= high-density lipoprotein. Note: At baseline, mode of transmission was unknown in 7.7%; smoking status was unknown in 20%; Hepatitis B and C status was unknown in 12% and 16% respectively; total cholesterol was missing in 7.8%, HDL cholesterol was missing in 31% and SBP was missing in 20% individuals.

Table-2: Number and incidence rates (95% CI) per 1000 PYFU of events by latest BMI category

Events	Latest BMI (kg/m ²) category						Overall
	<18.5	18.5-23	23-25	25-27.5	27.5-30	>30	
CVD	97 (6.7 [5.5-8.2])	578 (4.8 [4.4-5.2])	298(4.6 [4.0-5.1])	242(4.8 [4.2-5.4])	96(4.3 [3.5-5.3])	87(4.9 [3.9-6.0])	1398 (4.8 [4.6-5.1])
Diabetes	33 (2.3[1.6-3.2])	248 (2.0[1.8-2.3])	253 (4.0[3.4-4.4])	280 (5.6[4.9-6.3])	184 (8.5[7.3-9.8])	209 (12.2[10.6-13.9])	1207 (4.2[3.9-4.4])
Non-AIDS defining cancers (NADCs)	95 (7.9[6.4-9.6])	510 (5.1[4.7-5.6])	223 (4.0[3.6-4.6])	167 (3.8[3.3-4.5])	82 (4.2[3.4-5.3])	66 (4.2[3.2-5.3])	1143 (4.7[4.4-5.0])
BMI-cancers	12 (1.0[0.5-1.7])	75 (0.8[0.6-0.9])	32 (0.6[0.4-0.8])	31 (0.7[0.5-1.0])	13 (0.7[0.3-1.2])	21 (1.3[0.8-2.0])	184 (0.7[0.6-0.9])
All-cause mortality in males	260 (33.2 [29.3-37.5])	1138 (13.0 [12.3-13.8])	443 (8.4 [7.6-9.2])	333 (8.1 [7.3-9.0])	142 (8.7 [7.3-10.2])	102 (10.0 [8.2-12.2])	2418 (11.2 [10.8-11.7])
All-cause mortality in females	116 (16.8 [13.9-20.2])	256 (7.4[6.5-8.3])	94 (7.2[5.8-8.8])	66 (6.2[4.8-7.9])	33 (5.4[3.7-7.5])	42 (5.2[3.8-7.1])	607 (7.6[7.0-8.3])

Note: Table shows N (incidence rates per 1000 PYFU [95% confidence interval]). BMI-cancers are cancers previously shown to be strongly associated with BMI in multiple general population studies (see text for details). All-cause mortality rates shown separately by gender because in regression models there was a significant interaction by gender (P<0.001 for interaction term). PYFU= person years of follow-up.



